STILES (R. C.)

On the direct influence of medicinal and morbific agents + + + + + alph: bof.

ON THE DIRECT INFLUENCE

OF

MEDICINAL AND MORBIFIC AGENTS

UPON THE

MUSCULAR TISSUE OF THE BLOOD-VESSELS.

BY

R. CRESSON STILES, M. D.,

PHYSICIAN TO KINGS COUNTY HOSPITAL.

"Non fingendum, aut excogitandum, sed inveniendum."

READ BEFORE THE KINGS COUNTY MEDICAL SOCIETY,

Brooklyn, March 21st, 1865.

Box

NEW YORK:

PRINTED BY C. A. ALVORD,

15 VANDEWATER STREET.

1865.

ON THE

ACTION OF MEDICINES ON THE BLOOD-VESSELS.

THE following experimental researches were undertaken with the desire of extending, as far as possible, the influence of the anatomical generalizations of Bichat and the discoveries of modern histologists into the domain of practical medicine. The field of research was chosen as near as possible to that of practical medicine, in order that the results of experiment might be controlled by the experience of numerous observers among practitioners, instead of affording interest to the professed cultivators of abstract physiology merely, whose numbers are few, and with the tendency of whose pursuits whatever there is of magisterial influence and of practical conservatism in medical authority has but limited sympathy. Physiology is not far in advance of the position which chemistry held before the time of Lavoisier, but the movement which is drawing within the domain of the *Science of Vital Dynamics* the dependent science of Pathology (dependent, if legitimate scientific dependence exist at all), which leads the physician to seek in diseases the affections of an organism reacting in accordance with definite laws, rather than entities whose slightest variations in form and shade, in flying clouds of symptoms, are to be depicted in endless and useless detail, must affect also the classification and employment of therapeutic agents.

The several tissues of the body manifest varied and delicate differences of reaction to the agents employed in their study. These differences, due to molecular constitution, they doubtless possessed, with others of still greater delicacy, while forming a part of the living organism, rendering them subject to the variations of nutrition or function, which are the essential elements in all medicinal action. The influence of sulpho-cyanide of potassium and of upas upon the voluntary muscles, that of strychnine upon the afferent nerves, and that of wourara upon the motor nerves, give proof of relations subsisting between these substances and tissues

respectively which other tissues do not share, or in which they participate to but a slight extent. The power of carbonic oxide gas to paralyze the blood corpuscles, rendering them inert in hæmatosis, and that of a temperature of 115° Fahrenheit to paralyze and make rigid the voluntary muscles, while the same temperature leaves the motor nerves intact, lend further proof of the independent vital reactions of the different anatomical elements of the body. That these relations should be more familiar to physiologists than to practitioners is simply because they have been studied by the former; that many of the most familiar and most useful articles of the materia medica have like relations I propose to show. Similar considerations are applicable to the generation of diseases. The development of the Trichina Spiralis in the striated muscles exclusively, its presence ceasing, as I have seen it, with the upper third of the œsophagus, leaving the remainder of an apparently homogeneous canal uninfested, is a type of the mode in which other less vitalized morbific agents seek out certain tissues of particular physical or molecular constitution upon which to exert their activity.

Some of the most valuable revelations of experimental physiology have resulted from the study of the nervous system. The demonstration of the separate motor and sensory endowments of the anterior and posterior spinal nerves by Bell and Magendie, the determination of the powers of the principal centers of the cerebro-spinal system by Marshall Hall, Flourens and Longet, the recognition of the influence of the sympathetic upon nutrition, calorification, secretion, and the activity of the nervous centers by Bernard and Brown-Sequard, are examples of what has been accomplished in this field of research. It is characteristic of the nervous system, that its functional activity is brought into play by the simplest physical influences, rendering it particularly suited to experimental investigation. To the student of experimental physiology, or to the pathological anatomist, the fact cannot fail to present itself, that the office of the nervous system is rather of a passive nature, serving to call into action and regulate processes of far greater independence; both are led to regard the nervous system as an instrument whose wonderful harmonies are evoked by the play of forces external to itself. Not only has experiment shown that in death from inanition, while the blood loses over seven-tenths of its weight, and the muscles over four-tenths, the loss of the nervous system is less than one-fiftieth; but when we witness on post-mortem examinations the almost uniform complete integrity of the nervous system amid the wreck of other systems and the waste and decay of the rest of the body, and after death accompanied with the most violent nervous commotions, we are

forced to regard the nervous system as an instrument of sluggish nutritive changes, rather acted upon by the blood and the organs which it supplies, than itself generating its own forces and possessing the active nutrition necessary to such manifestations of energy. The nervous system has too long given sanctuary to all manner of fugitives from physiological law.

Except from our own individual sensations, we know nothing of nervous action but by muscular action, and it becomes exceedingly important therefore to determine whether the nervous system is not merely one of the instruments through which muscular activity is aroused, or whether physical and chemical agents do not exercise a direct and immediate influence upon muscular tissue through the medium of the blood.

Both Harvey and Haller denied the irritability or muscular contractility of the arteries. The contractile phenomena presented by the blood-vessels were believed by Bichat to be due to *tonicity*, an endowment different altogether from muscular contractility. "Respecting the final arterial ramifications," says Magendie, in 1822, "as the vessels which constitute them are so small as to be invisible, at least in a state of health, no one can either affirm or deny that they are irritable. It would follow from analogy, however, that they have no sensible movement. In cold-blooded animals, it is easy to see the blood circulating in these vessels, and even passing into the veins, but these same vessels give no sign of contraction." These views, thus attested, may be considered as those of the profession generally, till completely reversed by the revelations of the microscope. Since the discovery of the elements of the non-striated muscular tissue or fiber-cells by Kölliker, in 1847, and their recognition in the arteries and arterioles, the question has been set completely at rest. Numerous experimenters have studied the influence of mechanical irritation, of galvanism, of heat and cold, and of various medicinal substances upon the caliber of the vessels, and the rapidity of the circulation in the transparent tissues of the lower animals. The most real and decided of the recent triumphs of experimental physiology have been the result of researches upon the influence of the nervous system upon the circulation, as regulated by the muscular tissue of the blood-vessels, placing under the control of the experimenter the functional activity of various organs, and enabling him to produce at will the fundamental pathological phenomena of inflammation, hypertrophy, atrophy, and degeneration. But it is impossible to resolve these results into their elements. The solution of the simplest physiological problem is rendered difficult by the complexity of the conditions under which it is presented. Our present problem is to determine the influence of certain agents upon the living muscular tissue of the

blood-vessels, so as to be able to assign to this influence the part it plays in the involved phenomena of the action of these agents when used as remedies, or otherwise acting upon the human system; or, given a medicinal article, to determine whether, when brought into contact with the muscular tissue of a living artery, it produces its contraction, relaxation, paralysis, or a succession of these states; in what proportions used, and under what conditions these effects may be looked for with certainty. A step only towards its solution is still a step in advance.

The earliest and simplest observations made in this direction were on the obvious effects of cold and hæmostatic applications. By such observations, and by experiment, Hunter distinguished the elasticity of the arteries from their contractility, and recognized the persistence of the endowment of irritability long after death. He divided longitudinally arteries of different caliber, and determined, by measurement, the part in their contraction due to elasticity, and that due to physiological contractility, recognizing, before the microscope had shown that the smallest arteries are entirely wanting in elastic tissue, while their muscular tunic is well developed, that contractility has the largest influence upon the smallest arteries. He showed that contractility had no influence on the length of the arteries before minute anatomy had demonstrated the circular arrangement of their contractile elements. Kölliker experimented on the arteries of an amputated limb with a galvanic current, and produced contractions and constrictions of the popliteal and posterior tibial for an hour after the operation.

I have already alluded to experiments on the circulation in the transparent tissues of the lower animals, as seen by the microscope. These are now of vulgar performance, but it was not so when Schwann announced that he had produced successive contractions to one-third of their diameter in the mesenteric arteries of the toad by successive applications of cold water; or Ed. Weber reported having reduced the mesenteric arteries of the frog to one-sixth of their original diameter by an interrupted galvanic current. Numerous medicinal substances have since been tested in this manner, but the direct effect of the agents employed upon the muscular tissue is here involved with that upon the nerves, either directly or through reflex action, with the results of endosmose and exosmose, and with numerous other complications; and both the classes of experiments I have mentioned lack the quantitative determination, which is the surest basis of scientific generalization. Resort must be had to simpler methods.

The quantities of a liquid discharged through inert tubes of a caliber, such that the effects of friction are inconsiderable, are, other conditions

remaining the same, as the squares of the diameters of the tubes. As the tubes diminish in size, the effects of friction become more important, till, in capillary tubes, according to Poiseuille, the quantities discharged are inversely as the length of the tubes, and directly as the fourth power of their diameters. It follows, therefore, that a cause which would reduce the diameter of a capillary tube one-half, would reduce the amount of liquid discharged to one-sixteenth. Obviously the most accurate method of estimating the effect of delicate influences upon the caliber of the blood-vessels is that of measuring the amount of liquid they permit to pass through them under given conditions.

Poiseuille observed, also, that minute differences in the constitution of the liquids exerted a decided influence upon the rapidity of their flow through capillary tubes. Thus, the flow of serum was retarded by alcohol in such quantities as might be supposed often mingled with the blood during life, and that of the alcoholic serum accelerated by ammonia, and he argues that the beneficial effects of ammonia in drunkenness are due to this antagonistic influence. On injecting acetate of ammonia into the blood of a horse, he reduced the time of the round of the circulation from twenty-five and thirty seconds to eighteen and twenty-four seconds, and increased it to thirty-five and forty seconds with chloride of sodium. Iodide of potassium, nitrate of potassa, and chloride of ammonium, increased the rapidity of the circulation in animals, and of the liquid flow in inert tubes. Although his deductions from these experiments are manifestly unwarrantable, the influences which they reveal are important, and should not be neglected; they should not be allowed to vitiate the result of experiments on muscular irritability.

After numerous trials of apparatus and liquids in the endeavor to avoid sources of error, the following arrangement was adopted for a course of systematic experimentation. A reservoir is placed four feet above the operating table, to the bottom of which is adapted a long tube of caoutchouc terminated by the nozzle of a syringe for anatomical injection. The tube is coiled in another reservoir on the table, of a capacity of several gallons, into which water at any required temperature may be introduced, and lose heat slowly. The temperature of the liquid in this reservoir is that of the liquid discharged from the mouth of the tube, when the upper reservoir has been filled and the current allowed to flow. It is not raised above 110° Fahrenheit, nor allowed to fall below 100°. The liquid most used was a solution of sugar, of a specific gravity of from 1025 to 1030, perfectly neutral, not abstracting water from muscular fibers nor imbibing them, but permitting them to maintain their irritability

for a long period when immersed in it; not affecting the artery experimented on in its passage through it otherwise than mechanically. Blood and serum from the lower animals were employed occasionally to control the results obtained with the saccharine solution. The arteries experimented on were chiefly those of the umbilical cord, which the lying-in ward of a large hospital furnishes in abundance, and which are peculiarly adapted for the purpose. Other arteries were employed, and even whole organs of the lower animals, recently killed, were connected by their arteries with the apparatus, for the purpose of studying the capillary circulation.

The lower reservoir serves also as a water-bath, in which vessels containing the medicated solutions are immersed, their temperature being also that of the liquid flowing through the artery. The artery having been adapted to the tube, and the rate of flow through it measured, the current is arrested, the artery is suspended for a given time in the medicated solution, and the rate of flow is again measured. Or, the rate of flow having been measured, the substance to be tested is mingled in given proportion with the liquid in the upper reservoir, and thus allowed to act on the interior of the artery as in the circulation of the blood.

The arteries of the umbilical cord contain no elastic tissue, blood-vessels, nor nerves, but their muscular tunic is remarkably developed, imbedded merely in a loose connective tissue. No other large blood-vessel presents so completely the simple, uncomplicated phenomena of muscular contractility. Virchow, in his Cellular Pathology, has given a true description of the umbilical cord, showing the organized structure of the so-called gelatine of Wharton, and its likeness to the vitreous humor of the eye. He mentions the extraordinary development of the muscular coat of the umbilical arteries, and denies the existence of other blood-vessels than the main channels in its structure. Professor Simpson thus resumes the result of his investigations on the structure of the cord and placenta:—"Into the composition of these parts no capillaries, vasa vasorum, lymphatics, nor nerves are found to enter; hence, in human anatomy, we have these organs forming a large mass, and weighing on an average about two pounds, presenting a type of structure resembling that of some of the inferior zoöphytes." I have sought very carefully with the best powers of the microscope for nerves in the umbilical arteries, and have witnessed no appearance which would give the least suspicion of their existence, but the muscular fibers have their typical character and micro-chemical reactions. They may be beautifully isolated by maceration in dilute nitric acid, and, not being associated with elastic tissue, present the appearance they offer in the minutest arteries of the adult.

The arteries of the cord contract immediately on separation from its attachments, so that it is with difficulty that a liquid can be forced through them. In this state they appear like impermeable cords of a line in diameter. Hunter observed that they would retain this appearance for several days, till incipient decomposition produced complete relaxation. When relaxed completely, they are like flat bands of two lines in breadth, and transmit liquids in copious streams. The persistence of their irritability, though most probably not greater than that of adult arteries, fits them for prolonged experimentation.

1st. *On the Influence of Different Degrees of Heat on the Caliber of the Blood-vessels.*

The current flowing through a piece of umbilical artery was gradually heated, and as the following degrees, measured by a delicate Centigrade thermometer held in the stream, were reached, the following quantities were discharged in periods of three minutes each.

At 20 Centigrade,	68 Fahr.	3 fluid drachms.
At		86 "	4 " "
At		91 "	5½ " "
At 34°	"	93.2 "	7½ " "
At	"	98.6 "	11 " "
At 46	"	114.8 "	5 fluid ounces.

I have not determined the law of dilatation under different degrees of heat and varying rapidity of transition, but this series of observations proves, as did numerous others, that arterial dilatation is increased with elevation of temperature, and that the vascular irritability is most marked in the vicinity of blood-heat. An exceedingly interesting point is the limit of dilatation and the complete relaxation and paralysis of the muscular tissue at 115° Fahrenheit. This I have established by most careful observations, and the proof that the same phenomenon occurs in living animals also, I have given in an article on sun-stroke in the Boston Medical and Surgical Journal for June, 1864. When the temperature of the blood in rabbits has been raised to this point, the blood-vessels of the ears, turgid with dilated vessels and rapidly circulating blood, refuse to contract under the influence of cold and galvanic currents; when this symptom manifests itself, death soon ensues.

Water was heated to 55° Centigrade, and, as it cooled, portions of umbilical artery at the temperature of the room were immersed in it, at intervals of two degrees of temperature and for a minute of time. At

55° and 53° Cent., the artery became perfectly flaccid; at 51°, the flaccidity was not so complete, the artery possessed the slightest degree of tonicity; at 49°, the artery coiled up on immersion, and remained in a state of rigidity after it was withdrawn; at 47° it coiled up on immersion, but on exposure to the cold contracted more firmly; at 45° and 43°, no marked contraction ensued during immersion, but followed its withdrawal and exposure to the cold. These experiments prove that what is true of the striated muscular fiber, holds good also with the non-striated fiber of the arteries, both becoming rigidly contracted and paralyzed by a sudden elevation of temperature to the vicinity of 115° Fahrenheit.

In these experiments, no *active dilatation* could be perceived. The artery simply yielded to pressure from within, or to mechanical distention.

Evidence that heat has the power of relaxing the muscular coat of the finest arterioles was gained by experimenting on whole organs with the defibrinated blood of the lower animals. When a column of blood, four feet in height, connected with the artery of an organ—a kidney, for example—could not force a single drop from the veins, it was sufficient to immerse the organ in water at or above 100° Fahr., to admit free circulation through its capillaries, the rapidity of which rose with the elevation of temperature.

2d. *On the Effects of Medicinal Substances on the Caliber of the Blood-vessels.*

The medicinal substances subjected to experiment were chosen from the class of stimulants and sedatives, as most likely to manifest a direct influence on the muscular coat of the blood-vessels. In Wood's classification of the Materia Medica, the systemic stimulants proper are divided into the arterial, nervous, cerebral and spinal, and the systemic sedatives into the arterial, nervous and cerebral. Representatives of each of these classes were tested, and proof secured that many of them act directly upon the blood-vessels.

1. The *Arterial Stimulants*, according to Wood, are capsicum, oil of turpentine, certain ammoniacal preparations, of which carbonate of ammonia is chief, and phosphorus. Of these, carbonate of ammonia was deemed most worthy of study, from its undoubted medicinal powers, from the interest it has excited in theories of uræmic convulsions, of the coagulation of the blood, and of the causation of a low grade of fevers.

In one series of experiments with this substance to the liquid flowing steadily from the artery, at the rate of four and one-third fluid ounces every two minutes, the carbonate was added in the proportion of fifteen grains to the pint. The flow soon reached five fluid ounces in the same period,

and as the ammonia, or a mono-carbonate, evaporated from exposure to the air in a thin stream at the temperature of 100° Fahr. (the liquid having been poured back into the upper reservoir after each observation,) the quantity discharged fell to three and one-third fluid ounces. On adding an additional fifteen grains, the quantity rose to four fluid ounces. Here the play of the artery, under the varying doses of the carbonate, proved that we were dealing with physiological irritability, and not with mere physical or chemical phenomena.

To control these results and eliminate the influence shown by Poiseuille to be exerted by ammonia to hasten the current of liquid in inert tubes, arteries were immersed in solutions of the carbonate of different strength, the liquid flowing through them being the simple saccharine solution. An artery which discharged one and five-sixth fluid ounces per minute before it was suspended in a solution of the carbonate of the strength of a drachm to the ounce, after five minutes' immersion, discharged sixteen ounces per minute. An artery which, before immersion, discharged two ounces per minute, after immersion for three minutes in a solution of the strength of ten grains to the ounce, discharged eight ounces per minute. An artery which, before immersion, discharged two and one-sixth ounces per minute, after immersion for twenty minutes in a solution of the strength of two and a half grains to the ounce, discharged five ounces per minute. From the first experiment there resulted complete paralysis of the artery; from the others, relaxation merely, with conservation of irritability. Although the proportions of the carbonate were greater than those of the medicinal doses to the amount of blood in the circulation, still the arteries are undoubtedly more sensitive in a living animal than they were in these experiments.

The fact that ammonia possesses the power of relaxing the arteries having been proved, it remained to trace its influence upon the volume of the arteries, and the force and frequency of the pulse when administered as a remedy in disease. This study led me to several unexpected results. I found that I could administer thirty grains every fifteen minutes for an hour without the slightest influence on the pulse; that I could in no case produce its excitement, and that in several cases the result was its actual depression. It was strange that the medical authorities who testified to the stimulating properties of the sesqui-carbonate, when given in doses of ten grains every two hours, should have omitted to mention that it might be administered in doses of thirty grains every fifteen minutes, with no appreciable effect on the system. It was a disappointment to find the conclusions I had drawn from my experiments in the laboratory, falsified by further experi-

ments in the wards. I had not taken into consideration that carbonate of ammonia in solution is decomposed, according to Wood, "by most acids," "and by most salts with excess of acid," "by potassa, soda, and their carbonates; by lime-water and magnesia," and "by the soluble salts of lime;" that the gastric juice contains free hydrochloric and lactic acids, and that this secretion is seen to be poured out abundantly when the stomach of one of the lower animals is touched through a fistulous opening by a rod dipped in an alkaline solution; that, should the carbonate escape decomposition by the acids of the gastric juice, the alkalies and their carbonates would meet it in the blood, and destroy it often, as rapidly as it should be absorbed; that, should the carbonate be absorbed more rapidly than it could be decomposed by the gastric juice and the blood, it would probably not enter the arterial blood at all, but that portion which continued to be volatile, would escape from the system by the lungs, as sulphuretted hydrogen is known to do when sulphur-waters have been taken into the stomach. The systemic influence of the carbonate would therefore be that of a more stable compound of ammonia, as the muriate for example; its local influence would be one of irritation to the stomach, if not sufficiently diluted, and perhaps one of the free ammonia in the lungs. After taking a drachm of the carbonate, I caused all the air I expired for fifteen minutes to pass, in fine bubbles, through a linen tissue, kept saturated with dilute hydrochloric acid. The evaporated liquid yielded a notable amount of sal-ammoniac. As the linen had been previously soaked and washed in dilute hydrochloric acid, the ammonia could have had its source only in the expired air, and so large a proportion could not have been an ordinary physiological phenomenon. I concluded therefore that when large doses of carbonate of ammonia are taken, free ammonia escapes by the lungs. It is possible that the decided benefit with which the carbonate is administered in certain pectoral diseases, is due to this cause. In the experiments of Frerichs on uræmia, the injection of carbonate of ammonia into the blood was followed by convulsions, and the abundant escape of ammonia from the lungs. The question of the amount of ammonia expired, after large doses of the carbonate, should be settled by competent chemical authority.

The speedy precipitation of large and abundant crystals of the ammonio-magnesian or triple phosphate from the urina sanguinis, which, before the administration of the carbonate, had no such tendency, proved that an ammoniacal compound had found its way into arterial blood; but my experiments had shown that the stable ammoniacal compounds—the chloride, at least—had no influence in dilating the arteries, and thus the results of

clinical observation and those of experiment were reconciled; moreover, if I inspired for five minutes the air passing into a flask containing a solution of carbonate of ammonia, the excitement of the pulse was immediate and very manifest—but so was the irritation of the lungs.

That a general relaxation of the muscular tissue of the blood-vessels must produce those febrile phenomena called by physicians "general stimulation," can be shown to follow from well-known physiological laws.

The inconsistencies of the nervous theory of fever have been acknowledged by some of our best pathologists, who still cling to the doctrine of Cullen. How they can explain the effects of counter-irritation by the admission that there is in the body only a "certain amount of nervous influence," which when called to one part must forsake others, and yet trace to nervous influence the phenomena of fever, which they define as "a general disease affecting all the functions," has always seemed to me incomprehensible. The truth is, that a general excitement of the system cannot be a nervous manifestation simply. If one sense is developed or exercised, it is at the expense of the growth or activity of the other senses; the activity of the cerebrum calls off energy from the automatic nervous apparatus; pure nervous diseases are of a local character; all nervousness is non-febrile; severe injuries affecting the nerves are not immediately followed by fever. These and other facts of the same bearing are too patent, one would think, to the daily observation of physicians, to permit them to lay much stress on the accepted nervous theory of fever. In all nosologies, the pyrexiæ and neurotica form as distinct classes as nosological classification allows.

The necessary result of the existence in the blood of a substance acting simply to relax the muscular coat of the blood-vessels would be, in the first place, an increase of pressure in the arterioles and capillaries, in accordance with a well-known law of physics. This has been shown by Bernard to be the fact in several local circulations by cardiometric experiments. He has shown also that wourara, injected into the arteries of the sub-maxillary gland, produces paralysis of the motor nerves of the blood-vessels, with consequent increased rapidity of the circulation and escape of the blood from the vein in jets, corresponding with the pulses of the heart.* Should these phenomena of paralysis be systemic, instead of local, general venous distension would ensue, did not the heart beat more actively and the lungs transmit the crowding blood more rapidly. But the chief stimulus to the rythmical action of the heart is its supply of blood. Even after the medulla oblongata has been severed, we can control

* See Journal d'Anat. et de Physiol. 1864, p. 511.

the action of the heart by withdrawing blood from the system, and injecting it again into the blood-vessels; can thus arrest its motion, and restore it to action; or the same result can be effected by remitting or accelerating the movements of artificial respiration, thus diminishing or increasing the flow of blood to the heart through the lungs. The heart is the servant of the tissues and organs; it is from the capillary circulation mainly that its impulses are derived; hence, increased capillary circulation necessitates, when the links of the vital chain are still unbroken, increased action of the heart, and the flame of vital combustion may thus be fanned to fever heat.

That the common properties of muscular tissue are affected in our most characteristic febrile disorders is seen in the excessive prostration, muscular pains and weakness; in the slipping down in bed, and in the muttering delirium (one whose energies find no muscular expression); in the difficulty of swallowing, while the clearness of the intellect shows cerebral activity not seriously disturbed; in the tympanitic condition of the bowels, and the oppressed respiration. The increased pressure in the capillaries is marked by epistaxis, hæmmorhage from the bowels, petechiæ, and extravasations. After death from zymotic diseases, the softening of the organs generally, and particularly of those which are most vascular, is mainly due to the relaxation of the muscular tissue of the blood-vessels; is to these organs what the absence of cadaveric rigidity is to the limbs and trunk. The heart is found softened, not from a fatty degeneration, as I have repeatedly assured myself, but from a loss of tenacity of the muscular fibers entering into its composition. It shows the zymotic influence more than other striated muscles, because its unresting activity and rapid nutritive changes call for a full supply of blood, and receive a proportionate supply of its poison.

A materies morbi in the blood, confined there by the membranes of the blood-vessels (as all membranes have the power of secerning), would be in closest contact with the muscular tunic of the smallest vessels, and would exert upon them its paramount influence; but this admission is by no means essential to the theory advanced. The muscular activity of the blood-vessels is in constant play and delicate movement of adaptation to the pressure of the blood and the demands of the tissues, so that a poison diffused through the system would make its influence manifest by a disturbance of what is so nicely balanced, and on a tissue of such active nutrition and delicate reactions.

For these reasons, and abundant circumstantial evidence of their validity, which it would be tedious to detail, I would propose the following definition of fever: *An acute morbid activity of the general circu-*

lation and vital combustion, caused by the direct action of a blood-poison upon the muscular tissue of the blood-vessels.

It would require more time than the session could afford to spare, were I to enter at length upon the consideration of the objections which might be presented to this view of the generation of fever: on this head I will therefore be brief.

The School of Medicine at Paris teaches, through Monneret, that "disturbance of the nervous system appears to be the cause of the lesion of calorification and of the other febrile phenomena. How would it be possible to explain, in any other manner, the singular march which intermittents present, commencing and ending at fixed hours, and yielding with facility to sulphate of quinia. In the other pyrexiæ, specific causes appear to play the principal part, by acting on the nervous system. Everything leads to the admission that the vital forces, and the nervous system which is their support, are primarily affected. The study of the causes of the pyrexiæ seems to us to furnish a solid support to this hypothesis. Accordingly we see sometimes a local lesion, as a thorn buried in the flesh, sometimes a septic liquid, the virus of variola, of vaccinia, of marsh miasm, or the spontaneous alteration of the blood, provoke the febrile movement. At another time, it is to the disorganization of an organ that must be attributed the intense fever, which ceases only with the life of the patient." If it is on reasoning such as this that the hypothesis of the nervous origin of fever rests, its foundation is exceedingly insecure. How explain, says Monneret, in any other manner, the phenomena of intermittents? We would ask how the admission affords the least explanation? What recognized law of nervous action explains the commencement and cessation of intermittents at fixed hours, and their prevention by sulphate of quinia? Again, so far from the nervous system being the "support of the vital forces," comparative anatomy, embryology, and teratology teach plainly that the nervous system is an efflorescence, an exalted term, a perfection of organization, by no means fundamental to its manifestations of force. Again, "thorns buried in the flesh" are not a common cause of fever, and the "disorganization of an organ" must inevitably load the blood with the products of its decomposition. The remainder of Monneret's arguments are equally favorable to another hypothesis.

Wood, while lending a guarded adherence to the nervous theory of fever, and the doctrines of Brown and Darwin, confesses their inadequacy to explain some of the most marked characteristics of the febrile state. He says, "Along with the diminished exercise of nervous function, is necessarily a diminution of all the functions dependent on it. We may thus

partially explain the condition of the chill, but there is something more which we do not fathom; something, in which the chill of fever differs from other instances of nervous depression. Upon principles which have already been explained, the general prostration is succeeded by reaction, and the fever is thus established. But there is here also something more than reaction. There is the continued action of the cause—a diversified play of sympathies in one case, a widely prevailing influence from some unknown agent in another; and fever is not merely the *resilience* of the bowed-down system." That "widely pervading influence," that "something more than reaction," that "something more which we do not fathom," is a direct influence upon the muscular tissue of the blood-vessels. Wood, in combating the doctrines of Cullen, says, "there is no proof whatever of the existence of spasm of the extreme vessels. On the contrary, in the cold stage, they are in a state of collapse from their inability to receive and circulate the blood, and in the hot stage the vessels themselves are dilated, as is obvious from the fullness and redness of the surface." Precisely what condition may be meant here by "collapse from inability to receive and circulate the blood," we will not stop to inquire, but will note merely the admission that impeded transmission of blood by the extreme vessels is a phenomenon of the cold stage, while their increase of caliber marks the pyrexia. Before the bearing of the properties of muscular tissue upon the explanation of the phenomena of fever had presented itself, and while I was interested in merely tracing out the effect of remedies, I had recognized, as a purely muscular property, what has hitherto been attributed to nervous action, the contraction produced by the sudden application of agents capable of relaxing the muscular fibres. In speaking of the effects of immersion of an umbilical artery in water at different temperatures, I noted that an artery raised suddenly to a heat of 120.2°, Fahrenheit, manifested increased rigidity and firmer contraction; raised suddenly to 116.4°, Fahrenheit, it became somewhat contracted, but still more firm on exposure to the cold. Still, I had proved that a gradual elevation of temperature was attended by uninterrupted dilatation till the point of paralysis and complete relaxation was reached at 115°. I had noticed that on admitting suddenly the flow of a heated liquid into an artery the dilatation was preceded by a few minutes of contraction, and the same was true of the action of certain medicinal substances. The following series, taken from among my notes made in the laboratory, presents these facts in a clear light. The amount of a continuous flow from an artery was measured for successive periods of two minutes each. The temperature of the circulating liquid was 110°, Fahrenheit.

The following are the amounts:—

First period of two minutes,	3 fluid ounces.
Second " " "	$2\frac{2}{3}$ " "
Third " " "	$2\frac{1}{2}$ " "
Fourth " " "	$2\frac{1}{3}$ " "
Fifth " " "	$2\frac{1}{8}$ " "
Sixth " " "	$2\frac{2}{3}$ " "
Seventh " " "	$3\frac{1}{3}$ " "
Eighth " " "	$3\frac{1}{2}$ " "
Ninth " " "	$3\frac{1}{2}$ " "
Tenth " " "	4 " "
Eleventh " " "	4 " "

Here carbonate of ammonia was added in the proportion of fifteen grains to the pint to the liquid in the upper reservoir.

Twelfth period of two minutes,	5 fluid ounces.
Thirteenth " " "	5 " "
Fourteenth " " "	$3\frac{1}{2}$ " "
Fifteenth " " "	$3\frac{1}{8}$ " "
Sixteenth " " "	$3\frac{1}{3}$ " "
Seventeenth " " "	$3\frac{1}{2}$ " "
Eighteenth " " "	$3\frac{2}{3}$ " "
Nineteenth " " "	4 " "
Twentieth " " "	4 " "
Twenty-first " " "	4 " "

The temperature of the liquid had fallen five degrees in the forty-two minutes that the experiment lasted, and mono-carbonate of ammonia was evaporating during the eighteen minutes following its appearance in the artery.

That this mode of action is not confined to the blood-vessels, was proved in the following manner: From the small intestine of an animal just killed I cut rings by transverse sections. These I adapted to an instrument, by which the ring of intestine was maintained at such a degree of tension by one arm of a lever, to which was attached an elastic band, that the other, or long arm, would mark on the divided arc of a circle the slightest contraction or relaxation of the circular muscles of the intestinal ring. On immersing the ring in water above blood-heat, the long arm of the lever always marked a short period of contraction previous to the continued relaxation, which period of contraction was shorter as the temperature was higher. Similar phenomena of contraction followed

the immersion of the ring in solutions, which afterwards steadily dilated it. I found also that by successive increments of heat, as on several speedy withdrawals of the ring from the heated liquid after immersion, I could produce a more continuous contraction, from which at last the relaxation was marked and rapid. Should like phenomena occur in the arterioles of a living being, as the study of the circulation of the blood in transparent tissues would lead to believe, a poison thrown suddenly into the circulation, having the property of dilating the vessels, would at first produce their contraction or a stage of chill, while, if its admission were gradual, rigors would not appear. Or, successive increments of poisonous action in the blood-vessels, would either produce contraction or hold them in a passive, unchanging condition, till at last sudden and wide dilatation would be accompanied by the explosion of febrile disorder and paroxysmal symptoms in their greatest intensity. We have here an explanation of the so-called accumulation of excitability, the sudden discharge of which results in various paroxysmal attacks, to which the known laws of the nervous system afford no clue; we have at least analogies in the demonstrated laws of muscular action.

That the fever poison is always the same, or that the nervous system does not exert an important influence over febrile manifestations, no one will pretend. But that the cause of fever resides in, or acts through, the nervous system, is, from the preceding considerations, extremely improbable.

I would note also the looseness with which the terms *stimulation, sedation, exaltation, and depression of vitality*, are current in the profession. That the necessary consequences of paralysis, or impaired contractility of the blood-vessels, should be called stimulation, and the most complete disorder of function be denominated exaltation of vitality, shows an inadequacy or error in the interpretation of symptoms, the consequences of which must be exceedingly unfortunate.

Assimilation, growth, and development are the results of stimulation rather than disassimilation, atrophy, and combustion, and an inflammatory affection which leaves an organ shrivelled and cirrhosed, or a fever which wastes the system, and leaves it vacillating between life and death, is certainly not an exaltation of vitality.

In conclusion, I would claim the privilege of presenting the further results of experiment in this direction in a future communication.